

How Bacteria Give Cancer a Helping Hand

Two studies at the intersection of cancer and microbiome research explore how bacteria help tumors grow and spread.

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Tumors often get a lot of help in their efforts to survive and grow. Non-cancerous cells around a tumor can help it avoid attacks by the immune system, resist therapies that target them, and allow it to spread to other parts of the body. Researchers are now finding that some of these helpful neighbors aren't even human cells — they're bacteria.

The role that bacteria may play in promoting cancer is receiving more scientific attention. Two new studies from investigators at Fred Hutchinson Cancer Center reveal how bacteria infiltrate tumors and how they could be helping tumors progress and spread. The team also showed that the different microbial players in a tumor's microbiota (the full collection of microbes it carries) could influence how a cancer responds to treatment. The two papers, [one published November 15 in Cell Reports](#) and the [other published November 16 in Nature](#), focus on an oral bacterium called *Fusobacterium nucleatum*, which has been linked to colorectal cancer.

"What we're showing is that there are regions of the tumor that are heavily colonized by bacteria — micro-niche regions — and they differ functionally from regions that do not harbor bacteria," said Fred Hutch cancer microbiome researcher and study co-lead, [Susan Bullman, PhD](#), of the work outlined in the Nature study. "And these bacteria-rich regions have increased metastatic potential."

Bullman and her collaborator, Fred Hutch molecular microbiologist [Christopher D. Johnston, PhD](#), combined observations from tumors with lab-based experiments and small-molecule drug screens to show that *F. nucleatum* may shape conditions in tumors to keep them safe from immune attack and help them spread through the body. They discovered that some cancer therapeutics may work because they not only target tumor cells, but also the bacteria that are helping them.

The collaborators also found that other microbes — including the intestinal bug *Escherichia coli* — may render an anti-microbial and chemotherapeutic drug ineffective, which could shield both the tumor and *F. nucleatum* from treatment. These findings could help researchers develop new strategies to take down cancer by tackling its microbiome.

Bacteria Find Their Niche

“This work is at the intersection of cancer and microbiome research,” Bullman said. “There’s compelling emerging data to suggest that nearly all major cancer types harbor an intra-tumoral microbiota.”

And it’s not just in colorectal cancer tumors, where the association with bacteria may seem logical. Breast, pancreatic and lung tumors are also among the cancers shown to harbor microbial communities. More and more studies suggest that the tumor microbiota may shape tumor development, progression and response to treatment.

“When we think about a patient’s cancer, we usually think about the malignant cells,” Bullman said. “What are the mutations driving the cancer, and how can we target them? But what is underappreciated is that within these patient tumors there is a microbial ecosystem that can support cancer progression.”

Bullman and Johnston wanted to better understand the intimate connections between bacteria and the tumor microenvironment, and how these connections influence cancer-cell behavior. To do this, they adapted spatial transcriptomics, a leading-edge technology that allows researchers to detect where genes are turned on and off in slices of tumor tissue.

The investigators saw that a range of bacterial species, including *F. nucleatum*, live within oral cancer and colorectal cancers. But they also found that the bugs aren’t evenly distributed across the tumors.

“We observed bacterial hotspots, or micro-niches, which opened up a number of questions as to how these formed and might be impacting cancer biology,” Johnston said.

Bacteria Influence Tumor-Cell Behavior, Immune Microenvironment

Led by Jorge Galeano Niño, MD, PhD, the postdoctoral fellow who spearheaded the work, the team compared regions of oral and colorectal tumors that were rich in bacteria to those that lacked bacteria. They saw distinct differences.

“We saw that the regions colonized by bacteria were highly immunosuppressive,” Bullman said.

These areas had more of a kind of immune cell that can help tumors avoid attack by T cells, a type of immune cell that can kill cancer cells. (T cells are targeted by several [cancer immunotherapies](#).) The team also saw that fewer T cells had made their way into bacteria-rich regions.

“And when there were T cells [near bacteria-rich regions], there was upregulation of immune

checkpoint proteins,” Bullman said.

Immune checkpoint proteins restrain T cells from attacking cancer cells, and are targeted by checkpoint inhibitors, a type of [cancer immunotherapy](#). Although several checkpoint inhibitors are [approved for use in colorectal cancer](#), patients often see only limited effects against their tumors. Bullman and Johnston’s study might offer an explanation as to how a patient’s microbiota could influence whether their cancer responds to a checkpoint inhibitor.

The team also saw that regions with bacteria were more likely to be necrotic, with fewer dividing cells. It might sound like bad news for the tumor, but other research has shown that the tumor cells that spread and metastasize through the body often break away from necrotic areas. Cells can’t migrate while they’re rapidly dividing, so conditions that encourage cells to stop growing and start moving are conditions that can promote metastasis.

It looked like *F. nucleatum* could be encouraging tumor progression and immune evasion, but the data was correlative and couldn’t rule out the possibility that the microbes are just attracted to necrotic, already-immunosuppressed areas. To examine how bacteria may influence tumors, the team used tumor spheroids, which are tumor cells grown in 3D clusters in the laboratory.

To assess whether bacteria may promote an immunosuppressive environment, the scientists grew colorectal cancer spheroids with immune cells called neutrophils. Neutrophils crawled around and through tumor spheroids without bacteria. But when the investigators added *F. nucleatum* to the spheroids, they saw that neutrophils stopped moving and clustered within spheroids.

“The neutrophils migrated inside the spheroid and appeared trapped,” Galeano Niño said. “It supported what we saw in the patient spatial data: That there were neutrophils in the regions colonized by bacteria. That’s interesting because neutrophils negatively impact T-cell activity. This could perhaps explain what we’re seeing with the T-cell exclusion in those regions colonized by bacteria.”

The team also saw that tumor cells in the spheroids moved differently when bacteria were present. In spheroids without bacteria, the tumor cells moved en masse, which helped the spheroids grow larger, but didn’t help them release single cells capable of seeding new metastases.

“When bacteria were present, the cancer epithelial cells migrated as single cells — and they brought bacteria with them,” Bullman said.

The finding is in line with Bullman’s [previous work](#), in which she had shown that *F. nucleatum* often travels with colorectal cancer metastases.

But how exactly are bacteria interacting with and influencing cells? To learn more, the team adapted single-cell transcriptome sequencing technologies for bacteria, developing an approach they called INVADeSeq (Invasion Adhesion Directed Expression sequencing).

Using INVADeSeq, the team saw that tumor cells infected with bacteria ramped up genes

associated with cancer progression and metastasis. In oral tumor samples, the investigators saw that bacteria preferentially infected cancer epithelial cells and specific immune cell types within patients' tumors. Infected tumor cells were more likely to have turned on genes involved in responding to DNA damage, which is a hallmark of cancer.

"The functional work supports [the idea] that the bacteria have a direct role in shaping these micro-niche regions," Bullman said.

Tumor Microbiome Influences Drug Efficacy

If bacteria are promoting tumor progression, treating bacteria seems like an obvious way of also treating the tumor. Bullman's previous study supported this idea: when she treated mice engrafted with human tumor tissue with antibiotics, [this slowed the growth of colorectal cancers](#) positive for *F. nucleatum*.

"This raises the possibility of targeting specific members of the microbiota for patient cancer treatment," Bullman said.

But that proof-of-principle work relied on metronidazole, a drug that kills off a wide range of bacteria, even those that benefit us.

"You don't want to knock out all the beneficial microbes within a patient's microbiota — this needs to be very targeted," she said. "So, we designed a small-molecule screen of over 1,800 compounds to try and identify narrow-spectrum inhibitors of *F. nucleatum*."

Surprisingly, about 15% of the antimicrobials that meet this criterion were also chemotherapeutics — including 5-fluorouracil, or 5-FU, which is already routinely used to treat colorectal cancer.

The researchers found that *F. nucleatum* is extremely sensitive to 5-FU.

"That was really surprising to us," Bullman said. "It raises the possibility that part of 5-FU's treatment efficacy could be due to its antimicrobial activity."

But for many patients, 5-FU treatment doesn't prevent tumor growth. Could the tumor microbiota be contributing to this? When the team tested 5-FU against other bacterial strains taken from colorectal cancer samples, they saw that several, including a strain of *E. coli*, resisted its inhibitory effects. Growing this strain of *E. coli* with *F. nucleatum* protected *F. nucleatum* from 5-FU. (Another tumor-derived bacterial species they tested was unable to rescue *F. nucleatum* from the drug's effects.)

The researchers then found that *E. coli* protected colorectal cancer cells from 5-FU as well. The *E. coli* appeared to have a way of metabolizing the drug and minimizing its exposure to cancer cells or other bacteria.

“The findings show that intra-tumoral microbes are not innocent bystanders during disease progression, and suggest that the microbiota should be taken into consideration when thinking about optimal cancer treatments,” Johnston said.

Avenues to Explore New Treatments

The work further supports the idea that a tumor’s microbiota is an under-appreciated vulnerability and a potential treatment target. It appears that for some cancers, bacteria are important contributors to almost every step of tumor development and can even help shield it against treatment. Therapeutics that effectively modulate a tumor’s microbiota could help slow its growth as well as stave off metastasis or hobble cancer cells that have already spread.

The detailed analysis of bacterial species in both colorectal and oral tumors may also point to good oral health as an important way to help reduce cancer risk.

In addition to its cancer associations, *F. nucleatum* is linked to periodontal disease — and it wasn’t the only oral bacteria the team saw inside tumor cells from patients. Another oral bacterial genus linked to gum disease, called *Treponema*, also made its way inside tumor cells. These bacteria have also been linked to oral cancer, though the associations are less strong than *F. nucleatum*’s with colorectal cancer.

“There is a trend emerging of microbes that are traditionally associated with oral inflammatory disease being found in association with extra-oral and gastrointestinal cancers — which highlights the oral cavity as a breeding ground for pathogenic onco-microbes,” Johnston said.

In addition to allowing pathogens to spread to new areas of the body, it is possible that inflammation in the mouth, in the form of periodontal or endodontic disease, could be selecting for and encouraging the outgrowth of bacteria that are more specialized for growth in adverse conditions and capable of evading immune attack, he said.

Whether other tumors also harbor distinct bacterial micro-niches, and how these regions differ from non-colonized regions, are further questions Bullman and Johnston hope to answer. The team is exploring whether they can make tumors more responsive to immunotherapy or chemotherapy by manipulating their microbiomes. The first challenge will be developing strategies that are able to reach bacteria inside tumors. Further down the line, they hope to capitalize on the underlying biology of these tumor-homing microbes to develop novel therapeutic interventions, a strategy dubbed “bugs as drugs.”

By showing that microbes cluster in hard-to-reach areas of tumors, the same areas that are recalcitrant to current therapeutic regimens, the work clarified some hurdles that the team need to overcome in the development of new therapeutics.

“This holistic approach to assessing the tumor microenvironment, which is a multi-species ecosystem, will advance our understanding of cancer biology, and I believe will reveal new

therapeutic vulnerabilities in cancer,” Bullman said.

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